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Therapy of Fabry disease

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To the Editor: Referring to a Nephrology Forum by Siamopoulos et al [1] entitled "Fabry disease: Kidney involvement and enzyme replacement therapy" in a recent issue of *Kidney International*, we have to comment on two issues:

(*1*) Dr. Siamopoulos claims, "The availability of enzyme replacement therapy remarkably improves outcome of patients with Fabry disease."

This contention has not been proven formally by randomized controlled trials. The primary end points of two clinical trials showed disappearance of microvascular endothelial Gb3 deposits in renal biopsies [2] and decrease of neuropathic pain [3] after several weeks of enzyme replacement therapy. All other outcomes of the previously mentioned trials, such as decrease of resting global cerebral blood flow [4], clearance of deposits in endomyocardium and skin, quality of life, pain score [2], estimated glomerular filtration rate, Gb3 plasma levels, and cardiac conduction [3] have only been secondary end points, and thus, remain hypothesis generating. Other uncontrolled studies suggested a decrease of left ventricular hypertrophy [5], a reduction in QRS duration [6], an improvement in patients' New York Heart Association (NYHA) functional heart failure class [6], and an improvement of sweat function [7]. However, the design of these trials precludes valid conclusion on the efficacy of enzyme replacement therapy in Fabry disease.

(*2*) Dr. Siamopoulos also mentions "most heterozygote women remain asymptomatic and have a normal life span, only some expressing a few minor manifestations. Cardiac and renal manifestations in heterozygous women are usually lacking."

By way of contrast, two studies report that almost all females show multisystem involvement [8] and a decrease in life expectancy of about 15 years compared to the general population [9].

Although enzyme replacement therapy [2, 3] may hopefully reduce disease burden of female and male patients with Fabry disease, the improvement of many clinical end points still remains to be established. In the meantime, the clinical observations obtained in patients under enzyme replacement therapy should be considered more critically.

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Reply from the Author

As far as evidence-based medicine is concerned, I agree with Dr. Kleinert et al that the "outcomes" of patients with Fabry disease after enzyme replacement therapy (ERT) have not yet been confirmed in large randomized controlled trials. However, in my opinion, the rarity of this disorder should encourage us to take into consideration results from several independent investigators referring to a relatively small number of treated patients (as referenced by Dr. Kleinert et al), or even case reports [1], and the case of the first patient discussed in the Nephrology Forum, which clearly prove the clinical benefit of ERT.

It is suggested that ERT should be initiated in all patients with Fabry disease [2], and treatment should ideally begin as soon as clinical signs and symptoms are observed.

As I concluded in my discussion, I tried to raise awareness of the nephrologists in diagnosing the disease early.